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Neuropeptide-Y Both Improves and Impairs Delayed Matching-to-Sample Performance in Rats[1]

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THOMAS, J. R. AND S. T. AHLERS. *Neuropeptide-Y both improves and impairs delayed matching-to-sample performance in rats.* PHARMACOL BIOCHEM BEHAV 40(2) 417–422, 1991.—Neuropeptide-Y (NPY) was administered intracerebroventricularly to rats performing on delayed matching-to-sample (DMTS) to determine if NPY modulates short-term (working) memory. Rats administered saline demonstrated a characteristic DMTS delay gradient in which accuracy decreased as the delay interval between sample and comparison stimuli increased from 2 to 8 to 16 seconds. At 8- and 16-second delays, low doses of NPY (0.25 and 0.5 nmol/kg) increased matching accuracy. As doses increased from 1 to 16 nmol/kg, accuracy decreased in a dose- and delay-dependent manner. NPY effects were specific to working memory, since NPY did not affect accuracy of responses to the sample stimulus (reference memory). At higher doses, a greater decline in accuracy occurred when the correct stimulus was on the opposite side from the response on the previous trial compared to accuracy when the previous response was on the same side. These data show NPY may both improve and impair accuracy on DMTS and that some portion of impairment is due to proactive interference resulting from previous trials.

Neuropeptide-Y NPY Matching-to-sample Working memory Short-term memory Reference memory Memory modulation Proactive interference Rats

THERE is increasing clinical and experimental evidence that neuropeptide-Y (NPY), a 36-amino-acid sequence reported to be one of the most prevalent neuropeptides in the brain (1, 3, 7), plays an important role in modulation of memory. Clinically, the finding of reduced NPY immunoreactivity in the cortex and hippocampus of patients with Alzheimer's disease (4) as well as the presence of NPY like immunoreactivity in neuronal plaques (9) has implicated NPY in the pathogenesis of senile dementia of the Alzheimer's type. Experimentally, posttraining administration of NPY has been shown to enhance retention for both active and passive avoidance in mice (15, 24, 26). Administration of NPY prior to a retention test improves recall in mice, and NPY reverses amnesia induced by scopolamine or anisomysin (15). NPY administered directly into the forebrain hippocampal formation selectively enhances or impairs retention, depending upon the location of injection within rostral or caudal portions of the hippocampus (14). NPY has also been demonstrated to attenuate retention deficiency observed in aged mice (16).

As the research on memory modulation by NPY has focussed on long-term memory processes, the aim of the present study was to examine the effects of NPY on short-term or working memory. The highest concentrations of NPY and NPY receptors are in the hippocampus (6, 18, 25), a structure demonstrated to be important in working memory (10, 27, 28). In the present study, the effects of NPY on working memory were measured using a delayed matching-to-sample (DMTS) procedure in which rats were initially presented a sample stimulus and then, after varying delay intervals, required to correctly choose the sample stimulus from two comparison stimuli. In this task, a decline in accuracy is usually obtained as the delay interval between the sample and choice is lengthened, and the slope of the delay function is indicative of the rate of forgetting from working memory (22, 31, 32). The DMTS paradigm developed for rats in our laboratory is similar to others (5, 10, 11, 22), with the important addition that reference memory is also measured on each trial along with working memory (2,38). At the start of each matching trial, one of two lights located over each of two levers is illuminated as the sample stimulus. The animal is re-

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quired to respond correctly to the lever under the illuminated light to start a trial. After the delay interval, both lights are illuminated and the animal must respond to the lever under the previously illuminated light. This version of DMTS permits measurement of the rats' ability to attend to and discriminate the sample stimulus, which requires reference memory. Impairment of sample response accuracy would indicate nonspecific effects on attentional, motivational, or sensory-motor processes as opposed to specific impairments of working memory.

In addition, it was also of interest to examine possible mechanisms involved in modulation of working memory produced by central administration of NPY. Because proactive interference, that is, the influence of previous trials on following trials, has been demonstrated in disruption of performance in DMTS procedures with parameters similar to those of the present study (13, 30, 33, 37), data were recorded on a trial-by-trial basis for assessment of any proactive interference involvement in modulatory effects of NPY.

METHOD

Subjects

The subjects were three male Long-Evans rats maintained over the course of the study at 85% of their base (100%) weight. The subjects' base weight was adjusted upward during the study to account for growth; however, it was never allowed to exceed 380 g. The animals were individually housed in hanging home cages in an air-controlled unit. Water was available continuously in the home cage. They were maintained on a 12-h light/dark cycle starting at 6:00 a.m. They were always tested at the same time during the light portion of the cycle.

Apparatus

The subjects performed in a rat test cage 24.1 cm by 30.4 cm by 26.6 cm. Two response levers were mounted on the front wall, 5.0 cm above the grid floor and 3.8 cm from either of the side walls. A food tray was mounted 1.2 cm above the grid floor and in the center of the front wall equidistant from each of the levers. The tray was connected by a short tube to a pellet feeder, located behind the front wall, which could dispense 45-mg food pellets. A small light with a white lens cover was mounted 5.0 cm above both the right and left levers. A third response lever with a light located above it was located on the back wall, 5.0 cm above the floor. A speaker located behind the front wall was used for presentation of a 2800-Hz tone at approximately 40 dB. A house light was mounted on the top of the front wall. The rat cage was mounted inside a sound-attenuating environmental chamber. Experimental events were controlled and recorded by a computer system.

Matching Procedure

Sessions were conducted five days per week (M–F) with sessions terminating after completion of 180 trials or 60 minutes, whichever occurred first. The house light was illuminated during all sessions. At the start of each trial, the correct lever was cued by illumination of the light over *one* of the two levers on the front wall (sample stimulus). The rat was required to press the lever under the illuminated light. A response on the lever under the sample light turned off the light and started a delay interval. A response on the lever not under the sample light also turned off the light but was followed by a 5-second intertrial interval and the start of the next trial. A trial occurrence was recorded only if the rat correctly responded on the lever under the sample light. At the start of the delay interval, the light was illuminated over the single lever on the back wall. The delay interval was either 2, 8, or 16 seconds. A random order of delay intervals was presented in each session with the following constraints. Within a block of 60 trials, each delay interval appeared 20 times. Half of the trials at a particular delay interval began with the left light illuminated on the front wall, and the other half began with the right light illuminated. No more than two trials with the same delay could occur consecutively. The first response on the back wall lever following the completion of the delay interval resulted in turning off the back wall light, sounding a 2800-Hz tone, and illuminating *both* lights over the two front wall levers. Responding during the delay interval was maintained on a fixed-interval schedule. The value of the fixed-interval schedule was that of the nominal delay interval. The maintenance of responding on the back wall lever functioned to prevent the development of position bias or the adoption of simple mediating response patterns, such as standing in front of the appropriate front wall lever. The fixed-interval requirement also ensured that the rat was always positioned centrally in the back of the chamber at the termination of the delay interval. Following illumination of the two front wall lights and tone onset, a response on the front wall lever previously associated with the sample light was recorded as a correct matching response. A correct matching response produced a food pellet and turned off both front panel lights. If a response was made on the front panel lever not previously associated with the sample light (an incorrect matching response), both front panel lights were turned off. Following either a correct or an incorrect matching response, a 5-second intertrial interval preceded the beginning of the next trial. During the intertrial interval, only the house light was illuminated. Two months of daily sessions were conducted to establish stable performance on the matching procedure before animals were implanted with ventricular cannulae. Following surgery, another month of sessions was conducted before NPY administration.

Surgical Procedure

Once stable performance on the delay matching task was reached and maintained, rats were implanted with a chronic cannula placed into the lateral ventricle. Rats were anesthetized with pentobarbital sodium (40.0 mg/kg) and were placed in a stereotaxic apparatus. A 22-gauge guide cannula (Plastics One, Roanoke, VA) was chronically implanted in the lateral ventricle using the following stereotaxic coordinates from Paxinos and Watson (29): AP = −0.8, L = +1.3, from bregma. The depth or vertical location of the cannula was determined individually for each rat by the occurrence of a sudden drop in fluid level (phosphate-buffered saline solution, Sigma, St. Louis, MO) in a piece of 20-cm tubing attached to the guide cannula as it was slowly lowered into the ventricle. The guide cannula was anchored in place by cranioplastic cement which surrounded the guide cannula and four stainless steel screws threaded into the skull. At all times other than during injection, the guide cannula was sealed with a dummy cannula (Plastics One, Roanoke, VA).

Drug Administration

NPY (Peninsula Laboratories, Inc., Belmont, CA) was either freshly prepared in saline or used after freezing. NPY was prepared such that the volume of an administration was approximately 5.0 μl. Doses of NPY were 0.25, 0.5, 1.0, 2.0, 4.0, 8.0, and 16.0 nmol/kg. NPY or saline was injected intracerebroventricularly (ICV) through a 28-gauge injector cannula that,

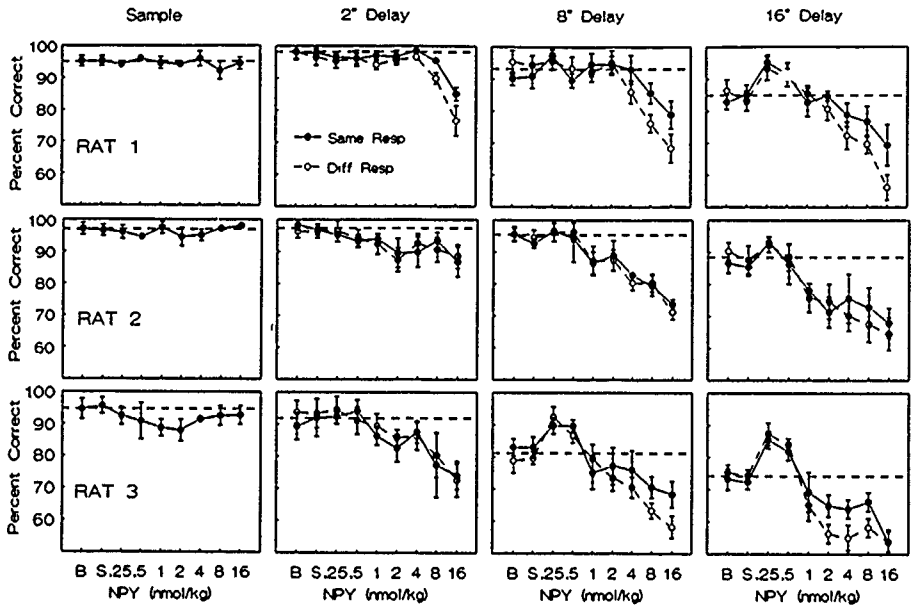

FIG. 1. Matching accuracy (percent correct) for sample stimuli (left column) and for comparison stimuli at three delays (other three columns) for three subjects (rows). For each section, accuracy is shown for baseline (B), saline (S), and increasing NPY dose sessions. Accuracy is plotted separately for trials in which the sample stimulus was on the same side as the response of the previous trial (Same Resp) and for trials in which it was on the opposite side (Diff Resp). The dotted line in each section represents mean baseline accuracy. Each data point represents the mean of at least three determinations, and the brackets indicate standard deviations.

when inserted, extended 1 mm beyond the tip of the guide cannula. The injector cannula was attached with 30 cm of polyethylene tubing to a microliter syringe (Hamilton, Reno, NV). A microsyringe pump (Harvard Apparatus, Model 22, South Natick, MA) was programmed to deliver the solution at a flow rate of 10 µl/minute. All doses were injected ICV 45 minutes before the start of a session. NPY was usually administered twice per week (Tuesdays and Fridays), and each dose was given to each subject three times in a different order. During other days of the week, the subjects performed on the DMTS baseline. At least one saline control session was obtained before and after the NPY regimen. In each sequential block of four administrations, one administration was always saline. Exactly which administration in a block was a saline control varied unsystematically throughout the NPY regimen and occurred in a different order for each subject.

RESULTS

Figure 1 shows the performance accuracy (percent correct) for each of the three subjects, both for the sample stimuli and for the comparison stimuli, at each of the three (2, 8, and 16 seconds) delays. For each of these conditions, accuracy is shown for baseline, saline control, and NPY sessions. The top row of Fig. 1 shows the sample and delay accuracy data of Rat 1. The middle row shows the accuracy data of Rat 2, and the bottom row shows the accuracy data of Rat 3. The accuracy data for all conditions is based on the same number of trials as the subjects completed all trials during NPY sessions.

The left column of Fig. 1 shows the accuracy of responding to the sample stimuli. Both baseline and saline session accuracies were higher than 95 percent correct. The dotted line across the top of each sample section represents the baseline accuracy and is included for comparison purposes. Increasing doses of NPY produced no consistent change in sample accuracy of any of the subjects, although there was a slight decline in accuracy at middle NPY doses for Rat 3. Sample accuracy appeared about the same for the highest NPY dose as it was for baseline conditions.

The next three columns of Fig. 1 show the accuracy of responding to the comparison stimuli for each of the subjects following delays of 2, 8, and 16 seconds. Again, the dotted line across each section represents baseline accuracy. Baseline accuracy was highest for the 2-second delay, lower for the 8-second delay, and lowest for the 16-second delay. For each of the three delays, matching response accuracy is plotted separately for those trials on which the comparison stimulus was on the same side as the response on the previous trial (Same Response) and for those trials on which the stimulus was on the opposite side as the response on the previous trial (Different Response). No consistent differences from baseline sessions were apparent during saline control sessions.

At the 2-second delay, lower doses of NPY had no effect, while higher doses produced a decline in matching accuracy, with each subject slightly sensitive to different dose values. At the 8-second delay, higher doses also produced a dose-dependent decline in matching accuracy, but of greater magnitude than the 2-second delay. Also, at the 8-second delay, Rat 3 clearly showed an increase in accuracy at doses of 0.25 and 0.5 nmol/kg. At the 16-second delay, an increase in matching accuracy is apparent for all three subjects at the low doses (0.25 and 0.5 nmol/kg) of NPY, while doses higher than 1.0 nmol/kg produced consistent decreases in accuracy.

It is also apparent from Fig. 1 that, at the longer delays, not only did the higher doses of NPY produce an impairment in accuracy, but the degree of impairment was influenced by the response made during the previous trial. Accuracy was lower at higher doses when the sample was on the opposite side from the

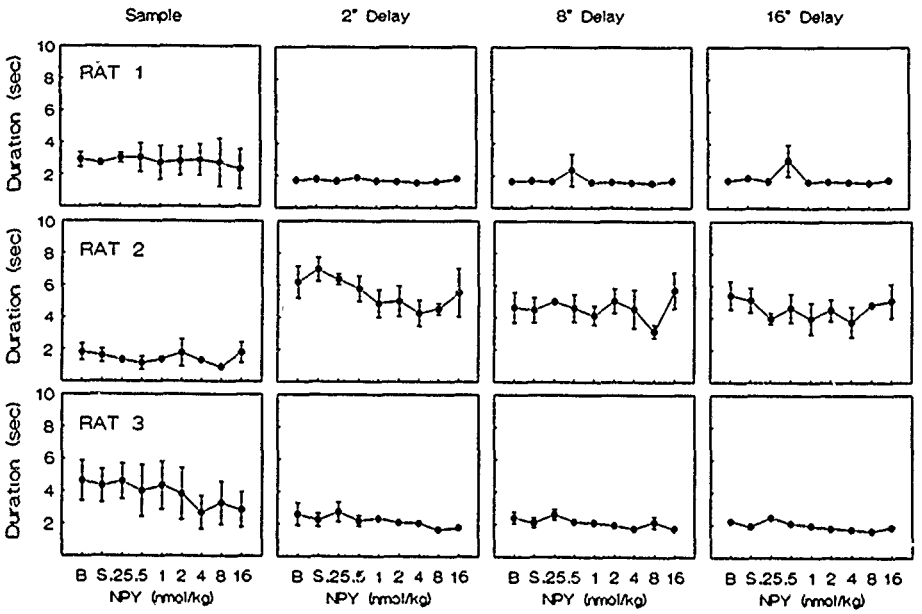

FIG. 2. Response latency (in seconds) for sample stimuli (left column) and for comparison stimuli at three delays (other three columns) for three subjects (rows). For each section, latency is shown for baseline (B), saline (S), and increasing NPY dose sessions. Each point represents the mean of at least three determinations, and the brackets indicate standard deviations.

response made on the previous trial (Diff Resp) than when the sample was on the same side as the previous response (Same Resp). The differential accuracy, as influenced by the previous response, was most apparent at the 16-second delay for all three subjects, and at the 8-second delay for two of the subjects. Responses during the previous trial appeared to have no discernable influence on increases in response accuracy obtained with lower NPY doses.

Figure 2 shows the response latencies for each subject for the sample stimuli and for the comparison stimuli at each of the three delays. No consistent differences as a result of NPY administration were observed in the latencies of responses to the sample stimuli or in the latencies of responses to the comparison stimuli.

DISCUSSION

During baseline and saline sessions, accuracy of responding to the sample stimuli at the beginning of each trial (reference memory) remained at more than 95 percent correct. This high level of accuracy was also obtained with the comparison stimuli at the 2-second delay. As expected, under baseline and saline conditions, accuracy related to working memory was influenced by the length of the delay interval between presentation of sample and comparison stimuli. With increasing delay, baseline accuracy declined, and the graded decline is comparable to working memory performance reported for rats on similar matching procedures (5, 10, 11, 22).

The observations of the present study indicate that NPY selectively modulates working memory as measured by the DMTS paradigm. Accuracy of responses to the comparison stimuli was affected by NPY, and those effects were delay dependent. Additionally observed performance changes were confined to matching accuracy measurements, as no consistent changes were seen in temporal measures of responding. The latency of responses to the sample stimuli did not change due to NPY administration, and latency of responses to the comparison stimuli was not systematically affected by NPY. No consistent changes were observed in reference memory, that is, sample response accuracy was unaffected, even at the highest doses. Except for a slight decrease in performance of Rat 3 at moderate doses, sample accuracies remained greater than 95 percent correct.

The lowest doses of NPY (0.25 and 0.5 nmol/kg) enhanced working memory above baseline levels, as shown by increased accuracy on the DMTS task. The observed enhancement of working memory with NPY is consistent with previous demonstrations showing facilitation of long-term memory as assessed by step-down footshock avoidance and T-maze footshock avoidance (15, 24, 26). Of the two performance-improving doses, there was a tendency for the smallest dose (0.25 nmol/kg) to be more efficacious than the 0.5 nmol/kg dose. These effects were most apparent at the longest delay (16 s), where baseline accuracy was lowest. The enhancement at longer delays may be the result of the delay length that places more emphasis on working memory and thus may be more sensitive to NPY, or the enhancement could be due to the lower baseline accuracy at longer delays that allows drug-induced improvement without the complication of ceiling effects. The latter view is supported by the observed increase in accuracy at the low doses at the 8-second delay for Rat 3, which showed much lower baseline accuracy at this delay than the other subjects. There was no demonstrated improvement for any subject in DMTS performance at the 2-second delay. Again, this may be due to either the minimal memory requirement or, more simply, to the higher baseline accuracy.

The higher doses of NPY (1.0–16 nmol/kg) impaired working memory. The only previous study of impairment of memory performance by ICV administration of NPY measured effects on long-term memory in overtrained mice (15). In that study, conditions for T-maze training with footshock avoidance were arranged to produce high recall scores that were impaired when tested one week following NPY administration. The decreases

in working memory accuracy in the present study were both dose and delay dependent. The magnitude of the accuracy decrement resulting from NPY administration was smallest at the 2-second delay and became greater at the 8- and 16-second delays. It was also clear that, at any delay, the larger the dose of NPY, the greater the impairment of accuracy. A direct interpretation of this decrease in accuracy is that it reflects an increased rate of forgetting from working memory. Although a portion of the accuracy impairment from NPY may be due to an increased rate of memory decay, it also appears that some of the decrement is due to proactive interference from previous trials. Under NPY, particularly at longer delays, the animals showed an increased interference from the response made on the previous trial. Such drug-induced susceptibility to proactive interference has been previously reported for similar DMTS procedures. For example, Dunnett et. al. (12) demonstrated that nicotine produced a greater decline in accuracy when the response on the previous trial was on the opposite side, compared to performance when the previous response was on the same side. An interesting aspect of the present study is that NPY induced proactive interference only at the higher doses at the longer delays, whereas no interference was discernable during baseline sessions or during increases in accuracy produced by lower doses. These data suggest that the effect of proactive interference resulting from NPY administration may only be revealed when there is weakened stimulus control for the target stimulus for that trial.

One of the significant findings with respect to the capability of NPY to modulate working memory is the biphasic effect obtained with increasing doses. At the 16-second delay, low doses of NPY increased matching accuracy, while higher doses decreased matching accuracy. This pattern was also obtained with Rat 3 at the 8-second delay. Differential dose effects have been reported previously for NPY and NPY fragments. For example, Flood et al. (15) found enhancement of retention of step-down passive avoidance and retention of a T-maze footshock avoidance task with moderate doses of NPY and lower retention measures at smaller or larger doses. Helig et al. (20) reported that an NPY fragment induced both increases and decreases in behavioral activity, depending on the dose. The biphasic responses of NPY obtained in the present study may be related to the heterogeneity of NPY receptors in the central nervous system. It is generally accepted that there are at least two different NPY receptor subtypes, designated Y_1 and Y_2 (35, 39, 40). It has been suggested that low doses of NPY only affect the Y_2 receptor and that higher doses may act on either the Y_1 or both Y_1 and Y_2 receptors (20), and selective involvement of these receptors may explain differential effects of NPY on behavior. Thus, to account for opposite, dose-dependent effects of NPY on behavior, it has been proposed that Y_2 receptors may mediate NPY-induced behavioral activation while Y_1 receptors mediate observed activity suppression (20) Additionally, the suggestion has been advanced of an active antagonistic receptor-receptor interaction between the two subtypes of NPY receptors (19), and such receptor interactions may also be considered in the modulation of behavioral effects with increasing doses. With respect to NPY effects on memory, evidence has established the existence of the two types of receptors in the hippocampal formation (35,36), although the hippocampus has a high density of Y_2 receptors relative to Y_1 receptors (34). A recent study on the improvement of retention in mice by NPY (24) proposed that the effects on memory retention are mediated through presynaptic Y_2 receptors, while other nonmemory-related effects of NPY are mediated through postsynaptic Y_1 receptors. That study demonstrated that shorter fragments of NPY, which bind only to the Y_2 receptor, produced memory enhancement similar to the effects observed with the entire peptide sequence. With different doses of NPY potentially able to mediate selective effects through differential activation of the two receptors, the biphasic results found in the present study may be interpreted in terms of selective NPY receptor mediation. This suggests that increased accuracy observed at the lower NPY doses is due to enhancement of working memory as mediated by Y_2 receptors, and impairment of performance with higher doses may be mediated by either overactivity at the Y_2 receptor or some combination of Y_1 and Y_2 receptor occupation. It is important to note that the decrement in accuracy observed at the higher doses of NPY does not result from behavioral suppression due to a predominant Y_1 effect, as all session trials were completed at higher doses.

Although the biphasic effects of NPY may be associated with differential activation of NPY receptors, it is possible that the effects may additionally be related to the specific anatomical location of those receptors. In this regard, Flood et al. (14) showed that injection of NPY into the rostral portion of the hippocampus and septum produced improved retention for T-maze performance, while injection into the caudal portion of the hippocampus and amygdala impaired retention. In addition to the importance of anatomical distribution of NPY receptors, one may also consider other functional aspects of NPY that may lead to biphasic effects. For example, opposite effects of low and high NPY doses on several neuroendocrine actions have been accounted for in part by the existence of NPY autoreceptors, preferentially activated by low doses of NPY, leading to reduced NPY release and thus to effects opposite to those obtained with higher doses of NPY (17).

At present, the exact mechanisms by which modulated activity of NPY receptors is able to affect memory are unknown. However, as there is strong evidence that excitatory amino acids, particularly glutamate, play an important role in normal hippocampal functioning associated with memory, it is important to note that NPY has been established as a potent presynaptic inhibitor of excitatory synaptic transmission in the rat hippocampus, probably by inhibition of glutamate release (8). The presynaptic excitatory inhibition appears to be related to NPY effects on calcium alteration but not to effects on adenylate cyclase (8,23), as found for peripheral presynaptic Y_2 receptors. Additionally, it has been proposed that NPY may induce some of its effects on memory by inhibition of presynaptic gamma amino butyric acid release from basket cells in the hippocampus that normally inhibit the firing of pyramidal cells containing glutamate, which results in enhanced neural activity of pyramidal cells (25). Considering that the majority of NPY receptors in the hippocampus are of the Y_2 presynaptic type, the focus of experimental manipulations on NPY fragments and receptor antagonists that selectively mediate effects through Y_2 receptors may help further the understanding of mechanisms by which NPY may both improve and impair memory functioning.

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